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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.
09/277,229	03/26/99	CITRUN M	A-581

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U.S. PATENT OPERATIONS/NAO
DEPT. 430, M/S 27-4-A
AMGEN INC.
ONE AMGEN CENTER DRIVE
THOUSAND OAKS CA 91320-1799

EXAMINER	
RAO,M	
ART UNIT	PAPER NUMBER
1652	5

DATE MAILED: 08/14/00

Please find below and/or attached an Office communication concerning this application or proceeding.

Commissioner of Patents and Trademarks

U.S. G.P.O. 1999 460-693

Office Action Summary

Application No.	Applicant(s)
09/277,229	Citron et al.
Examiner	**Group Art Unit**
Manjunath N. Rao	1652

☒ Responsive to communication(s) filed on *May 22, 2000*

☐ This action is **FINAL.**

☐ Since this application is in condition for allowance except for formal matters, **prosecution as to the merits is closed** in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11; 453 O.G. 213.

A shortened statutory period for response to this action is set to expire *3* month(s), or thirty days, whichever is longer, from the mailing date of this communication. Failure to respond within the period for response will cause the application to become abandoned. (35 U.S.C. § 133). Extensions of time may be obtained under the provisions of 37 CFR 1.136(a).

Disposition of Claim

☒ Claim(s) *1-21* is/are pending in the applicat

Of the above, claim(s) *1-9, 15, 16, and 21* is/are withdrawn from consideration

☒ Claim(s) *13* is/are allowed.

☒ Claim(s) *11 and 17-20* is/are rejected.

☒ Claim(s) *10, 12, and 14* is/are objected to.

☐ Claims _____ are subject to restriction or election requirement.

Application Papers

☐ See the attached Notice of Draftsperson's Patent Drawing Review, PTO-948.

☐ The drawing(s) filed on _____ is/are objected to by the Examiner.

☐ The proposed drawing correction, filed on _____ is ☐ approved ☐ disapproved.

☐ The specification is objected to by the Examiner.

☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. § 119

☐ Acknowledgement is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d).

☐ All ☐ Some* ☒ None of the CERTIFIED copies of the priority documents have been

☐ received.

☐ received in Application No. (Series Code/Serial Number) _____.

☐ received in this national stage application from the International Bureau (PCT Rule 17.2(a)).

*Certified copies not received: _____

☐ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. § 119(e).

Attachment(s)

☒ Notice of References Cited, PTO-892

☐ Information Disclosure Statement(s), PTO-1449, Paper No(s). _____

☐ Interview Summary, PTO-413

☐ Notice of Draftsperson's Patent Drawing Review, PTO-948

☐ Notice of Informal Patent Application, PTO-152

— SEE OFFICE ACTION ON THE FOLLOWING PAGES —

DETAILED ACTION

Election/Restriction

1. Restriction to one of the following inventions is required under 35 U.S.C. 121:

   I. Claims 1-9 and 21, drawn to isolated polynucleotides encoding , vectors and host cells, classified in class 435, subclass 69.1.

   II. Claims 10-14 and 17-20, drawn to an isolated polypeptide, classified in class 435, subclass 226.

   III. Claims 15-16, drawn to antibody, classified in class 530, subclass 389.1.

2. The inventions are distinct, each from the other because of the following reasons:

3. Inventions II and I are patentably distinct from each other. The polypeptide of group II, the polynucleotide of group I, each comprise amino acid sequences and nucleotide sequences which are chemically unrelated, do not require each other for practice; have separate utilities, such as use of the group II polypeptide to catalyze a peptide cleavage reaction versus the use of polynucleotide in a hybridization reaction and are subject to separate manufacture and sale. The groups have acquired separate status in the art and separate fields of search.

4. Inventions II and III are patentably distinct from each other. The polypeptide of group II, the antibody of group III, each comprise unrelated amino acid sequences, do not require each other for practice; have separate utilities, such as use of the group II polypeptide to catalyze a

proteinase reaction versus the use of antibody in protein purification techniques and are subject to separate manufacture and sale. The groups have acquired separate status in the art and separate fields of search as further evidenced by their separate classification.

5. Inventions III and I are patentably distinct from each other. The antibody of group III, the polynucleotide of group I, each comprise amino acid sequences and nucleotide sequences which are chemically unrelated, do not require each other for practice; have separate utilities, such as use of the group III antibody in a immunoprecipitation reaction versus the use of polynucleotide in a hybridization reaction and are subject to separate manufacture and sale. The groups have acquired separate status in the art and separate fields of search.

6. The inventions are distinct, each from the other because of the following reasons: Because these inventions are distinct for the reasons given above and have acquired a separate status in the art as shown by their different classification, restriction for examination purposes as indicated is proper.

7. During a telephone conversation with Nancy Oleski on 6-20-2000 a provisional election was made with traverse to prosecute the invention of group II, claims 10-14 and 17-20. Affirmation of this election must be made by applicant in replying to this Office action. Claims

1-9, 15-16 and 21 are withdrawn from further consideration by the examiner, 37 CFR 1.142(b), as being drawn to a non-elected invention.

8. Applicant is reminded that upon the cancellation of claims to a non-elected invention, the inventorship must be amended in compliance with 37 CFR 1.48(b) if one or more of the currently named inventors is no longer an inventor of at least one claim remaining in the application. Any amendment of inventorship must be accompanied by a petition under 37 CFR 1.48(b) and by the fee required under 37 CFR 1.17(I).

Claim Objections

9. Claims 10 and 12 are objected to because of the following informalities: Claims 10 and 12 depend on claims 9 and 1 respectively, which belong to non elected group. Appropriate correction is required.

9a. Claim 14 is objected to because of the following informalities: Claim 14 recites few amino acid fragments more than once, for example amino acids 1-420 is recited twice. Appropriate correction is required.

Claim Rejections - 35 USC § 112

10. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claim 11 is rejected because, the invention appears to employ novel vectors. Since the vectors are essential to the claimed invention, they must be obtainable by a repeatable method set forth in the specification or otherwise be readily available to the public. The claimed plasmids' sequences are not fully disclosed, nor have all the sequences required for their construction been shown to be publicly known and freely available. The enablement requirements of 35 U.S.C. § 112 may be satisfied by a deposit of the plasmids. The specification does not disclose a repeatable process to obtain the vectors and it is not apparent if the DNA sequences are readily available to the public. Accordingly, it is deemed that a deposit of these plasmids should have been made in accordance with 37 CFR 1.801-1.809.

It is noted that applicants have deposited the organisms containing the vectors, but there is no indication in the specification as to public availability. If the deposit was made under the terms of the Budapest Treaty, then an affidavit or declaration by applicants, or a statement by an attorney of record over his or her signature and registration number, stating that the specific strain has been deposited under the Budapest Treaty and that the strain will be irrevocably and without restriction or condition released to the public upon the issuance of the patent, would satisfy the deposit requirement made herein.

If the deposit has <u>not</u> been made under the Budapest treaty, then in order to certify that the deposit meets the criteria set forth in 37 CFR 1.801-1.809, applicants may provide assurance

or compliance by an affidavit or declaration, or by a statement by an attorney of record over his or her signature and registration number, showing that:

1. during the pendency of this application , access to the invention will be afforded to the Commissioner upon request;

2. all restrictions upon availability to the public will be irrevocably removed upon granting of the patent;

3. the deposit will be maintained in a public repository for a period of 30 years or 5 years after the last request or for the effective life of the patent, whichever is longer; and

4. the deposit will be replaced if it should ever become inviable.

11. Claim 11 is rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention. Claim 11 of the instant application is drawn to a polypeptide selected from a group consisting of polypeptides which includes splice variants.

Claim 11 is rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for polypeptides with SEQ ID NO:4, 5 and 6, does not reasonably provide enablement for splice variants of the same. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make the invention commensurate in scope with this claim.

Claim 11 encompasses polypeptides which form due to improper splicing of the mRNA precursors coding for the polypeptides with SEQ ID NO: 4-6. It is well known in the art that splice variants form due to improper splicing event of mRNA precursor molecule wherein a single amino acid may be added or deleted at the junctions of two exons resulting in altered final amino acid sequence of the polypeptide. In order to determine if one has a splice variant of a polypeptide a detailed map of the genomic clone is necessary along with identification of the exons and introns such that one skilled in the art would exactly know where the splice occurs with respect to the final amino acid sequence. Without the information of exons and introns and specific nucleotide numbers where an intron/exon starts and ends it would not be possible for one skilled in the art to determine a splice variant solely based on cDNA information. However, in this case the disclosure is limited only to the cDNA sequence information of the polypeptides with SEQ ID NO:4-6.

The specification does not support the scope of the claims which encompass all the splice variants of polypeptides with SEQ ID NO: 4-6 because the specification does **not** establish/provide :(A)the genomic DNA sequences encoding the polypeptides with SEQ ID NO:4-6 (B) the identification of introns and exons with nucleotide position numbers on the genomic clone; (C) a rational and predictable scheme for isolation and characterization of splice variants with the desired biological activity and function; (D) examples and sequence information of at least one such splice variant with the desired biological activity and function;

and (E) the specification provides insufficient guidance as to which of the infinite possible choices is likely to be successful.

Thus, applicants have not provided sufficient guidance to enable one of ordinary skill in the art to make and use the claimed invention in a manner reasonably correlated with the scope of the claims broadly including splice variants that have not yet been discovered. The scope of the claims must bear a reasonable correlation with the scope of enablement (In re Fisher, 166 USPQ 19 24 (CCPA 1970)). Without sufficient guidance, determination of having the desired biological characteristics is unpredictable and the experimentation left to those skilled in the art is unnecessarily, and improperly, extensive and undue. See In re Wands 858 F.2d 731, 8 USPQ2nd 1400 (Fed. Cir, 1988).

12. Claim 17 is rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention. Claim 17 of the instant application is drawn to a pharmaceutical composition of beta-secretase polypeptide.

Claim 17 is rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for beta-secretase polypeptides with SEQ ID NO:4, 5 and 6, does not reasonably provide enablement for a pharmaceutical composition of a beta-secretase polypeptide. The specification does not enable any person skilled in the art to which it

pertains, or with which it is most nearly connected, to make the invention commensurate in scope with this claim.

Claim 17 is directed to a pharmaceutical composition comprising beta-secretase enzyme. It is well known in the art that for any agent to be used as a pharmaceutical composition, an effective dose of that specific agent and the disease/disorder/ condition against which it is used is required. Further when new agents are to be used in a pharmaceutical composition, there is also a need for the demonstration that the agent would be effective in the said dosage against a specific disease/disorder/condition in an art accepted animal model experiment/s. Without such information one skilled in the art would be unable to make and use the claimed invention without further experimentation. However, in this case the specification fails to provide such details.

The specification does not support the scope of the claim directed to a pharmaceutical composition of beta-secretase because the specification does **not** establish/provide :(A)the effective amount of beta-secretase needed for use in a pharmaceutical composition(B) against what disease/disorder/condition the pharmaceutical composition is effective; and (C)demonstrate the desired effect of use in an art recognized animal model experiment.

Thus, applicants have not provided sufficient guidance to enable one of ordinary skill in the art to make and use the claimed invention in a manner reasonably correlated with the scope of the claim broadly including pharmaceutical composition of beta-secretase. The scope of the claims must bear a reasonable correlation with the scope of enablement (In re Fisher, 166 USPQ 19 24 (CCPA 1970)). Without sufficient guidance, determination of having the desired

characteristics is unpredictable and the experimentation left to those skilled in the art is unnecessarily, and improperly, extensive and undue. See In re Wands 858 F.2d 731, 8 USPQ2nd 1400 (Fed. Cir, 1988).

13. Claims 11 and 18 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

Claims 11 and 18 are directed to polypeptide fragments corresponding to amino acid sequence of SEQ ID NO:4, variants of SEQ ID NO:4, in which 1-50 amino acids have been changed, allelic variants, splice variants and derivatives of the polypeptide with SEQ ID NO:4-6. Claims 11 and 18 are rejected under this section of 35 USC 112 because the claims are directed to a genus of polypeptides derived from SEQ ID NO:4-6, including modified polypeptide sequences, modified by at least one of deletion, addition, insertion and substitution of an amino acid residue in SEQ ID NO:4 that have not been disclosed in the specification. No description has been provided of the modified polypeptide sequences, allelic variants or the splice variants encompassed by the claim. No information, beyond the characterization of SEQ ID NO:4-6 has been provided by applicants which would indicate that they had possession of the claimed genus of modified polypeptides. The specification does not contain any disclosure of the function of all the polypeptide sequences derived from SEQ ID NO:4-6, including fragments and allelic variants

and splice variants within the scope of the claimed genus. The genus of polypeptides claimed is a large variable genus including peptides which can have a wide variety of functions and with the potentiality of generating many different antibodies. Therefore many functionally unrelated polypeptides are encompassed within the scope of these claims. The specification discloses only a single species of the claimed genus which is insufficient to put one of skill in the art in possession of the attributes and features of all species within the claimed genus. Therefore, one skilled in the art cannot reasonably conclude that applicant had possession of the claimed invention at the time the instant application was filed.

Applicant is referred to the revised interim guidelines concerning compliance with the written description requirement of U.S.C. 112, first paragraph, published in the Official Gazette and also available at www.uspto.gov.

Claim Rejections - 35 USC § 102

14. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless --
>
> (a) the invention was known or used by others in this country, or patented or described in a printed publication in this or a foreign country, before the invention thereof by the applicant for a patent.
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.
>
> (e) the invention was described in a patent granted on an application for patent by another filed in the United States before the invention thereof by the applicant for patent, or on an international application by another who has fulfilled the requirements of paragraphs (1), (2), and (4) of section 371(c) of this title before the invention thereof by the applicant for patent.

15. Claims 11 and 18 are rejected under 35 U.S.C. 102(a) as being anticipated by Chrysler et al. (WO 98/26059, dated 6-18-1998) or Chapman et al. (EP-855444 A2, dated 7-29-1998). This rejection is based upon the public availability of a printed publication. Claims 11 and 18 of the instant application are drawn to an isolated polypeptide from the group consisting of a polypeptides with SEQ ID NO: 4-6, a biologically active (activity being ability to cleave the APP, Swedish mutation peptide EVKMDAEF between methionine and aspartic acid residues) fragment of any of the SEQ ID NO:4-6 or a biologically active polypeptide with 1-50 conservative amino acid changes or an allelic variant or splice variant or a derivative of SEQ ID NOS:4-6. Chrysler et al. or Chapman et al. disclose an enzyme with an identical activity of cleaving APP. The references disclose a DNA sequence that encodes such an enzyme and amino acid sequence of a fragment of such an enzyme. From the functional and structural aspects disclosed in the reference it is highly likely that the enzyme, polypeptide sequence is identical to that of the instant application (99.9% identical to the amino acid disclosed by Chapman et al. see enclosed sequence comparison). Since there is no limitation placed on the number of changes that can be present in the polypeptide sequence, SEQ ID NO:4, for a allelic/splice variant or a derivative and since the applicant has not disclosed such amino sequences, Examiner believes that the enzyme and polypeptide disclosed in the reference is the same as that of the instant application. Thus Chrysler et al. anticipate claims 11 and 18 of this application as written. Since the Office does not have the facilities for examining and comparing applicants' protein with the protein of the prior art, the burden is on the applicant to show a novel or unobvious difference

between the claimed product and the product of the prior art (i.e., that the protein of the prior art does not possess the same material structural and functional characteristics of the claimed protein). See *In re* Best, 562 F.2d 1252, 195 USPQ 430 (CCPA 1977) and *In re* Fitzgerald et al., 205 USPQ 594.

16. Claims 11 and 18 are rejected under 35 U.S.C. 102(b) as being anticipated by Chrysler et al. (WO 96/40885, dated 12-19-1996). This rejection is based upon the public availability of a printed publication. Claims 11 and 18 of the instant application are drawn to an isolated polypeptide from the group consisting of a polypeptides with SEQ ID NO: 4-6, a biologically active (activity being ability to cleave the APP, Swedish mutation peptide EVKMDAEF between methionine and aspartic acid residues) fragment of any of the SEQ ID NO:4-6 or a biologically active polypeptide with 1-50 conservative amino acid changes or an allelic variant or splice variant or a derivative of SEQ ID NOS:4-6. Chrysler et al. disclose an enzyme with an identical activity of cleaving APP. The reference discloses a DNA sequence that encodes such an enzyme and amino acid sequence of a fragment of such an enzyme. From the functional and structural aspects disclosed in the reference it is highly likely that the enzyme, polypeptide sequence is identical to that of the instant application. Since there is no limitation placed on the number of changes that can be present in the polypeptide sequence, SEQ ID NO:4, for a allelic/splice variant or a derivative and since the applicant has not disclosed such amino sequences, Examiner believes that the enzyme and polypeptide disclosed in the reference is the same as that of the

instant application. Thus Chrysler et al. anticipate claims 11 and 18 of this application as written. Since the Office does not have the facilities for examining and comparing applicants' protein with the protein of the prior art, the burden is on the applicant to show a novel or unobvious difference between the claimed product and the product of the prior art (i.e., that the protein of the prior art does not possess the same material structural and functional characteristics of the claimed protein). See *In re* Best, 562 F.2d 1252, 195 USPQ 430 (CCPA 1977) and *In re* Fitzgerald et al., 205 USPQ 594.

17. Claims 11 and 18 are rejected under 35 U.S.C. 102(e) as being anticipated by Chrysler et al. (US 5,744,346, dated 4-28-1998, filed 6-7-1995) or Anderson et al. (US 5,942,400 dated 8-24-1999, filed 6-7-1996). This rejection is based upon the public availability of a patent to another. Claims 11 and 18 of the instant application are drawn to an isolated polypeptide from the group consisting of a polypeptides with SEQ ID NO: 4-6, a biologically active (activity being ability to cleave the APP, Swedish mutation peptide EVKMDAEF between methionine and aspartic acid residues) fragment of any of the SEQ ID NO:4-6 or a biologically active polypeptide with 1-50 conservative amino acid changes or an allelic variant or splice variant or a derivative of SEQ ID NOS:4-6. Chrysler et al. disclose an enzyme with an identical activity of cleaving APP. The reference discloses a DNA sequence that encodes such an enzyme and amino acid sequence of a fragment of such an enzyme. From the functional and structural aspects disclosed in the reference it is highly likely that the enzyme, polypeptide sequence is identical to

that of the instant application. Since there is no limitation placed on the number of changes that can be present in the polypeptide sequence, SEQ ID NO:4, for a allelic/splice variant/derivative and since the applicant has not disclosed such amino sequences, Examiner believes that the enzyme and polypeptide disclosed in the reference is the same as that of the instant application. Thus Chrysler et al. anticipate claims 11 and 18 of this application as written. Since the Office does not have the facilities for examining and comparing applicants' protein with the protein of the prior art, the burden is on the applicant to show a novel or unobvious difference between the claimed product and the product of the prior art (i.e., that the protein of the prior art does not possess the same material structural and functional characteristics of the claimed protein). See *In re* Best, 562 F.2d 1252, 195 USPQ 430 (CCPA 1977) and *In re* Fitzgerald et al., 205 USPQ 594.

Claim Rejections - 35 USC § 103

18. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 11 and 17-20 rejected under 35 U.S.C. 103(a) as obvious over Chrysler et al. (WO 96/40885, dated 12-19-1996). Claims 11 and 17-20 are directed to beta-secretase enzyme polypeptides, a pharmaceutical composition, a derivative, and fusion polypeptide with IgG constant domain or a fragment thereof. Chrysler et al. has been discussed above in paragraph 15.

Combining the teachings of Chrysler et al. with the high level of knowledge existing in the art at the time the invention was made it would have been obvious to one of ordinary skill in the art to make a pharmaceutical composition of the polypeptide of claim 11 and a fusion protein using the IgG constant domain or its fragment. One would have been motivated to do so as Chrysler et al. teach that beta-secretase is responsible for the pathogenic cleavage of the beta-amyloid precursor protein that has been implicated in the causation of Alzheimer's disease. One of ordinary skill in the art would have a reasonable expectation of success since Chrysler et al. provide compositions comprising beta-secretase enzyme.

Therefore it would have been *prima facie* obvious to one of ordinary skill in the art to have performed the claimed invention.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(f) or (g) prior art under 35 U.S.C. 103(a).

Allowable Subject Matter

19. Claims 13 and 14 (after overcoming the objection) are allowable.

20. The following is a statement of reasons for the indication of allowable subject matter: Following a diligent search it was determined that the prior art neither teaches nor suggests a polypeptide or its fragments (claimed in claim 14) that is 100% identical to the amino acid sequence depicted in SEQ ID NO:4 claimed in claim 13.

21. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Manjunath Rao whose telephone number is (703) 306-5681. The Examiner can normally be reached on M-F from 6:30 a.m. to 3:00 p.m. If attempts to reach the Examiner by telephone are unsuccessful, the Examiner's supervisor, P.Achutamurthy, can be reached on (703) 308-3804. The fax number for Official Papers to Technology Center 1600 is (703) 305-3014. Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is (703) 308-0196.

PONNATHAPU ACHUTAMURTHY
SUPERVISORY PATENT EXAMINER
TECHNOLOGY CENTER 1600

Manjunath N. Rao

August 10, 2000